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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

TATSUYA NAKAI, ET AL. : EXAMINER: M. P. CHUI

SERIAL NO: 10/589,247 :

FILED: AUGUST 14, 2006 : GROUP ART UNIT: 1616

FOR: EXTERNAL PREPARATION :

DECLARATION UNDER 37 C.F.R. 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Makoto Kanebako, state that:

1. I have a Doctorate of Pharmacology degree from the Hoshi University, which I received in 2003.
2. I have been employed by KOWA CO., LTD for 24 years as a Researcher in the field of external pharmaceuticals.
3. I am an inventor of this application.
4. I am familiar with the above-identified application.
5. The following experiments were performed by me or under my direct supervision.
6. The following experiments show the effects of different concentrations of menthol in a poultice composition on the skin permeability of pitavastatin calcium.
7. In these experiments, the poultice was prepared as described in Example 7 of this application ranging the amount of menthol as shown in the Table below. The skin

permeability of pitavastatin calcium was tested in the same manner as Test Example 2 in this application.

8. The content of each composition and the results that were observed are shown in the Table below:

Raw Material	Additional Example 1	Additional Example 2	Example 7	Additional Example 3	Additional Example 4
Pitavastatin calcium	0.50	0.50	0.50	0.50	0.50
L-menthol	0.05	0.50	2.00	5.00	12.00
PEG400	10.00	10.00	10.00	10.00	10.00
Concentrated glycerin	15.00	15.00	15.00	15.00	15.00
D-sorbitol solution (70%)	25.00	25.00	25.00	25.00	25.00
Kaolin	3.00	3.00	3.00	3.00	3.00
Carmellose sodium	4.00	4.00	4.00	4.00	4.00
Crosslinker	0.75	0.75	0.75	0.75	0.75
Sodium edetate	0.10	0.10	0.10	0.10	0.10
Sodium polyacrylate	2.00	2.00	2.00	2.00	2.00
Partially neutralized poly acrylic acid	2.00	2.00	2.00	2.00	2.00
Tartaric acid	0.25	0.25	0.25	0.25	0.25
Polysolvate 80	0.1	0.1	0.1	0.1	0.1
Purified water	Total amount 100g	Total amount 100g	Total amount 100g	Total amount 100g	Total amount 100g
pH	about 7.0				
Permeability coefficient (10^{-4} cm/h)	0.5	1.2	2.9	2.2	0.3

9. The data shown in the attached Declaration, when considered in view of the comparative data presented in Table 4 of the specification, shows that at concentrations 0.1 to 10 % by mass, e.g., 2 to 10% by mass of (B) increased the permeability coefficient. I understand the U.S. Patent Office has cited to a number of documents to argue that the use of terpenes, such as menthol, in combination with pitavastatin, atorvastatin, or their salts would have been obvious because menthol has been used in the past by some to increase skin absorption of other types of active agents. However, the effects shown by the collective data would not have been reasonably predictable for the pitavastatin, atorvastatin, or salts thereof based on Sawayanagi, Hidaka, and Dasseux even with the other references cited by the U.S.

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Patent Office as the ability of a substance to improve percutaneous absorption of a target drug greatly varies depending on the type of substance and the drug, and there is no way to reasonably predict what effect a particular substance will have on a particular target drug.

10. All statements made herein are true to my knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Makoto Kaneko
Signature

October 4, 2010
Date